Divergent Hemodynamic and Hormonal Responses to Varying Salt Intake in Normotensive Subjects

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Blood pressure responses to 1 week of low-salt (20 mmol sodium/d) and high-salt (300 mmol sodium/d) intake were investigated in a single-blind randomized study in 163 white, nonobese normotensive subjects (65 women and 98 men; mean age, 38±1.2 years). The individuals were classified as salt sensitive when mean arterial blood pressure rose by at least 5 mm Hg during high-salt intake, as salt resistant when mean arterial blood pressure changed by less than 5 mm Hg, and as "counterregulator" when mean arterial blood pressure fell by at least 5 mm Hg during the high-salt diet. Reexamination of 31 subjects showed that this approach to the testing of salt sensitivity was reliable and reproducible. Thirty subjects (18.4%) were classified as salt sensitive, 108 (66.3%) as salt resistant, and 25 (15.3%) as counterregulators. Multiple regression analysis revealed that age, body weight, and family history of hypertension contributed significantly to the change in blood pressure after the diets. Salt sensitivity was more frequent in older subjects and in those with a positive family history of hypertension. An increase in blood pressure after salt restriction was more likely in younger individuals and in those with a negative family history of hypertension. Plasma renin activity and plasma aldosterone concentrations were lower in salt-sensitive compared with salt-resistant and counterregulating subjects. The rise in plasma renin activity during salt restriction was most pronounced in counterregulating subjects. Plasma norepinephrine concentrations were not different among the groups. Plasma levels of atrial natriuretic peptide increased during high-salt intake in all groups, the rise being most pronounced in salt-sensitive subjects. The increase in blood pressure during salt restriction in counterregulating subjects may be partially due to an overstimulation of the renin-angiotensin system. The exaggerated response of the secretion of atrial natriuretic peptide to high-salt intake in salt-sensitive subjects may point to an impaired capability of the kidney to excrete a salt load. (*Hypertension*. 1993;22:331-338.)

KEY WORDS • **sodium, dietary** • **renin** • **aldosterone** • **norepinephrine** • **atrial natriuretic peptide** • **hypertension, sodium-dependent**

Considerable evidence has been accumulated over the past decades linking sodium chloride to the pathogenesis of essential hypertension.[1-3] However, in recent years the strength of this linkage and consequently the possible benefits of dietary salt restriction have been questioned,[4-6] partially because of the results of the INTERSALT study.[7] It has been assumed recently that the effect of a concerted health care program directed toward lowering salt intake of the general population would be extremely small.[6] The blood pressure response to sodium chloride is heterogeneous, at least during relatively short-term changes in salt intake. Salt sensitivity, defined as a significant rise in blood pressure when individuals switch from a low to a high sodium chloride intake, is seen in a considerable number of patients with essential hypertension and, although less frequent, in normotensive subjects.[8] On the other hand, some individuals increase their blood pressure with sodium depletion[9,10] and therefore could be at higher risk when ingesting a salt-restricted diet.

Little attention has focused so far on this issue. This may partially be due to the design of most of the previous studies dealing with salt sensitivity in which subjects reacting to low-salt intake with no change or a rise in pressure were termed salt resistant and usually analyzed together. In the present study, the heterogeneity of blood pressure responses to changes in sodium chloride intake were investigated in a large number of nonobese normotensive subjects and analyzed with regard to age, sex, body weight, family history of hypertension, and hormonal changes.

Methods

Subjects and Study Protocol

The study was approved by the Ethics Committee of the University Hospital, and written informed consent was obtained from all participants. We studied 163 white, nonobese individuals with a body mass index of less than 28 kg/m^2. The subjects were recruited by advertisements in local newspapers and were paid for their participation. A medical history was obtained, and

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TABLE 1. Baseline Data

Variable	All	Salt-sensitive	Salt-resistant	Counter-regulation
n	163	30 (18.4%)	108 (66.3%)	25 (15.3%)
Men/women	98/65	14/16	65/43	19/6
Age (y)	38±1.2	46.4±3.2	36.3±1.4*	35.4±2.9*
Body weight (kg)	70.9±0.9	67.1±2	71.7±1.1*	71.9±2.5
MAP (mm Hg)	87.1±0.6	89.3±1.4	86.3±0.7	87.6±1.8
Heart rate (bpm)	66.2±0.7	66.9±1.5	66.6±0.9	63.5±1.9
Urinary Na^+ (mmol/24 h)	167.5±4.1	154.5±6.7†	167.6±5.2	182.7±11.1
Urinary K^+ (mmol/24 h)	79.5±2	78.9±4.2	78.4±2.4	85.1±5.3
Urinary Na^+/K^+ ratio	2.24±0.06	2.06±0.11	2.29±0.08	2.26±0.16

MAP, mean arterial pressure; bpm, beats per minute.
*$P<.05$ vs salt-sensitive.
†$P<.05$ vs counterregulation.

a physical examination as well as routine laboratory tests were performed. All subjects taking any medication or exhibiting a previous or current medical history of hypertension, cardiac or renal diseases, diabetes, or hyperlipidemia were excluded from the study. Ambulatory sitting blood pressure had to be less than 140/90 mm Hg, measured on three different occasions. The subjects were asked specifically for parental history of hypertension, and when possible the family physician also was contacted. Parental history of hypertension remained questionable in 12 subjects, who were excluded from data analysis that looked for genetic disposition as a determinant of salt sensitivity. A positive family history of hypertension was defined as at least one hypertensive parent.

A low-salt diet containing 20 mmol sodium daily was given to all subjects for 2 weeks according to a 7-day rotating meal plan. The diet was prepared by the dietary kitchen of the hospital and contained 75 to 90 g protein, 220 to 350 g carbohydrates, 90 to 105 g fat, 75 mmol potassium, and 30 mmol calcium. The amount of calories remained constant for the whole study period and was calculated for individual needs. The subjects came daily to the hospital to obtain a warm lunch and to receive the food for the following dinner and breakfast. Drinking of tap water and of tea and coffee ad libitum was allowed, but the subjects were instructed to avoid all other beverages.

Low- and high-salt diets were given for 1 week each in a single-blind, randomized crossover fashion. During the low-salt diet (20 mmol sodium/d), the subjects received 32 placebo capsules per day. During the high-salt diet (300 mmol sodium/d), they received 32 capsules per day containing 0.5 g NaCl each. Compliance with the diets was assessed by measuring 24-hour urinary electrolyte excretion on days 5, 6, and 7 of each dietary period. Additional 24-hour urine collections were performed on the day before the dietary periods were started (baseline data). On this day as well as on the last day of each dietary period, the subjects were studied in the morning (7:30 AM) after an overnight fast. After a 30-minute rest, blood pressure and heart rate were measured with subjects in the sitting position for 1 hour at 5-minute intervals using automated blood pressure monitors with integrated printers (Boso Oscillomat, Bosch & Sohn GmbH, Jungingen, Germany). The mean of the 12 blood pressure readings was taken for further analysis. Mean arterial pressure (MAP) was calculated by adding one third of the pulse pressure to the diastolic pressure. Blood was drawn for biochemical measurements after the last blood pressure reading. Serum concentrations of sodium, potassium, creatinine, and uric acid were measured by standard laboratory methods. Plasma renin activity (PRA) and plasma concentrations of aldosterone and atrial natriuretic peptide (ANP) were measured by radioimmunoassay.[11-13] Plasma concentrations of norepinephrine were determined by a radioenzymatic method.[14] In women who menstruated, the study was begun 10 days after the menstrual period had started. Women taking oral contraceptives or oral or transdermal estrogen were excluded from the study.

Subjects were divided into three groups according to their changes in MAP between low- and high-salt intake. An individual was classified as salt sensitive when MAP rose by at least 5 mm Hg during high-salt intake compared with low-salt intake, as salt resistant when MAP changed by less than 5 mm Hg, and as "counterregulator" when MAP fell by at least 5 mm Hg during high-salt intake. The reproducibility of this procedure was tested in 31 individuals in whom the study was repeated 3 months later.

Statistical Analysis

Statistical analysis was performed by analysis of variance, the Mann-Whitney *U* (Wilcoxon) test, and Wilcoxon's matched pairs signed rank test, as appropriate. Pearson's correlation coefficients were used to examine the relation between variables and among changes in variables. In addition, multiple regression analysis was performed with the change in MAP as dependent variable and with baseline MAP, age, sex, body weight, and family history of hypertension as independent variables. Statistical significance was considered at a value of $P<.05$. Results are expressed as mean±SEM.

Results

From a total of 163 subjects, 30 (18.4%) were classified as salt sensitive, 108 (66.3%) as salt resistant, and 25 (15.3%) as counterregulators (Table 1). Salt-sensitive subjects were significantly older than salt-resistant individuals and counterregulators and had a lower sodium excretion at baseline. Salt-sensitive subjects had

TABLE 2. Response to Low- and High-Salt Diet in Salt-Sensitive and Salt-Resistant Subjects and in Counterregulators

Variable	Salt-sensitive (n=30)		Salt-resistant (n=108)		Counterregulation (n=25)	
	Low NaCl	High NaCl	Low NaCl	High NaCl	Low NaCl	High NaCl
Body weight (kg)	65.9±2*	67.0±2*†	70.4±0.9	71.5±1†	70.4±2.4	71.8±2.4†
MAP (mm Hg)	83.1±1.2‡	91.2±1.3†§	85.1±0.6	84.6±0.6	89.6±1.5	82.3±1.4†
Heart rate (bpm)	66.3±1.4	64.2±1.6	67.2±1	63.5±0.9†	65.0±2.2	60.6±2.2‖
Serum Na^+ (mmol/L)	137.5±0.4	138.8±0.3†	137.6±0.2	139.2±0.2†	137.6±0.3	138.6±0.2†
Serum K^+ (mmol/L)	4.4±0.1	4.2±0.1	4.3±0.1	4.2±0.1	4.3±0.1	4.2±0.1
Serum uric acid (mmol/L)	95.8±5.0	75.6±3.4†	100.8±1.7	82.3±1.6†	99.6±5.2	83.8±3.2†
Serum creatinine (μmol/L)	79.6±1.2	76.9±1.4¶	86.5±0.9	79.9±1.1†	89.0±1.5	81.2±1.8‖
Urine volume (mL/24 h)	1692±110	1989±123†	1618±51	2006±55†	1426±72	1806±126†
Urinary Na^+ (mmol/24 h)	15.9±1.3	285.6±4.4†	17.1±0.9	291.6±3.2†	15.4±1.6	294.6±5.2†
Urinary K^+ (mmol/24 h)	72.5±2.3	67.5±2.8¶	75.4±1.4	72.1±1.5‖	74.5±3	69.4±2.8
Urinary Na^+/K^+ ratio	0.22±0.02	4.42±0.19†	0.23±0.01	4.25±0.12†	0.22±0.02	4.38±0.16†
Creatinine clearance (mL/min)	95.2±3.7	104.6±4.2†	100.4±2.3	110.7±2.4†	100.4±3.8	111.7±4.6†

MAP, mean arterial pressure; bpm, beats per minute.
*$P<.05$, salt-sensitive vs salt-resistant.
†$P<.001$, low NaCl vs high NaCl.
‡$P<.001$, salt-sensitive vs counterregulation.
§$P<.001$, salt-sensitive vs counterregulation and salt-resistant.
‖$P<.01$, low NaCl vs high NaCl.
¶$P<.05$, low NaCl vs high NaCl.

a lower body weight than salt-resistant individuals, and they tended to have a higher blood pressure at baseline than the other groups (Table 1). The difference in body weight between salt-sensitive and counterregulating subjects was not statistically significant.

MAP for all subjects did not change between low-salt intake (85.4±0.5 mm Hg) and high-salt diet (85.5±0.6 mm Hg). MAP for the different groups is shown in Table 2. During salt restriction, heart rate rose significantly compared with salt loading in the salt-resistant and counterregulating groups but not in the salt-sensitive subjects. During high-salt intake, body weight, serum concentration of sodium, urinary volume, and sodium excretion as well as creatinine clearance increased, whereas serum concentrations of creatinine and uric acid decreased compared with the low-salt diet in all groups (Table 2). The mean as well as the individual data for urinary sodium excretion demonstrate good dietary compliance of the subjects.

Of the 163 subjects studied, 98 were men and 65 women. Women subjects were slightly but not significantly older than men. Their blood pressure and body weight were lower and heart rate was higher than in the men (Table 3). Men exhibited a significant decline in MAP during high-salt intake, whereas women showed a significant rise. Women were more likely to be salt sensitive (24.6%) than counterregulators (9.2%), whereas in men counterregulation was observed in 19.4% and salt sensitivity in only 14.3%. However, these differences in gender were not significant when multiple regression analysis was applied.

Fifty-four subjects with a positive and 97 subjects with a negative family history of hypertension could be identified. In 12 subjects parental history with regard to blood pressure remained unknown, so they were excluded from this part of the analysis. Individuals with a positive family history were significantly younger than those with a negative family history (Table 4). The only other difference was seen in blood pressure. MAP at baseline was significantly higher in those with a positive than in those with a negative family history (89.1±1.1 vs 85.9±0.8 mm Hg, $P<.01$). During salt restriction, MAP fell slightly although not significantly in the subjects with a positive family history but remained constant in the others (Table 4). Subjects with a positive family history were more likely to be salt sensitive (25.9%) than counterregulators (7.4%), whereas in those with a negative family history counterregulation was observed in 20.6% and salt sensitivity in only 14.4%.

When different age groups were compared, MAP was found to increase with age. Baseline MAP was 85.8±0.8 mm Hg in subjects younger than 30 years, 87.0±1.1 mm Hg in subjects between 30 and 50 years, and 89.6±1.3 mm Hg in subjects older than 50 years (for

TABLE 3. Response to Low- and High-Salt Diet According to Gender

Variable	Men (n=98)		Women (n=65)	
	Low NaCl	High NaCl	Low NaCl	High NaCl
Age (y)	36.4±1.5		40.5±2	
Body weight (kg)	75.8±1*	77.3±1*†	60.5±1	61.7±1†
MAP (mm Hg)	87.5±0.6*	86.5±0.7*‡	82.1±0.8	84.0±1‡
Heart rate (bpm)	65.2±1§	61.1±0.9*†	68.9±1.7	66.5±1.1‖
Urinary Na^+ (mmol/24 h)	16.4±1	293.6±3.3†	17.0±1	285.6±3.8†
Urinary K^+ (mmol/24 h)	76.1±1.6	72.1±1.6†	72.8±1.6	69.4±1.8‡

MAP, mean arterial pressure; bpm, beats per minute.
*$P<.001$, men vs women.
†$P<.001$, ‡$P<.05$, low NaCl vs high NaCl.
§$P<.05$, men vs women.
‖$P<.01$, low NaCl vs high NaCl.

TABLE 4. Response to Low- and High-Salt Diet According to Family History of Hypertension

Variable	Family history of hypertension			
	Positive (n=54)		Negative (n=97)	
	Low NaCl	High NaCl	Low NaCl	High NaCl
Age (y)	33.0±1.6		40.7±1.7*	
Body weight (kg)	70.3±1.6	71.4±1.6†	69.7±1.2	70.7±1.2†
MAP (mm Hg)	86.8±1*	87.6±1*	84.6±0.7	84.7±0.7
Heart rate (bpm)	67.0±1.2	63.8±1.2†	66.8±1	63.1±1†
Urinary Na^+ (mmol/24 h)	17.1±1.1	286.5±4.9†	14.8±0.9	290.1±3.1†
Urinary K^+ (mmol/24 h)	73.2±2.2	71.6±2.1	75.1±1.4	70.1±1.6†

MAP, mean arterial pressure; bpm, beats per minute.
*$P<.05$, subjects with vs subjects without genetic predisposition.
†$P<.001$, low NaCl vs high NaCl.

<30 vs >50 years, $P<.01$). In the younger and intermediate age groups, blood pressure remained fairly constant during the different diets (Table 5). In the older age group, MAP rose significantly during high-salt intake when compared with sodium restriction. Subjects older than 50 years of age were more likely to be salt sensitive (37.2%) than counterregulators (11.6%), whereas in subjects less than 30 years of age, counterregulation was observed in 17.9% and salt sensitivity in only 12.8%. Serum creatinine concentrations were not significantly different among the age groups. However, creatinine clearance progressively decreased with age (Table 5).

Baseline MAP and the change in MAP between the low- and high-salt diets were significantly correlated to age ($r=.225$, $P<.01$ and $r=.236$, $P<.01$, respectively). However, baseline MAP was not related to the change in MAP after the different diets. At baseline, body weight and body mass index were positively related to MAP ($r=.372$, $P<.001$ and $r=.375$, $P<.001$, respectively). The change in MAP between the low- and high-salt diets was inversely related to baseline body weight ($r=-.202$, $P<.01$), but it was not related to body mass index. Baseline sodium and potassium excretions as well as baseline creatinine clearance were not related to baseline MAP or to the diet-induced changes in blood pressure.

When multiple regression analysis was performed with the difference in MAP between the low- and high-salt diets as dependent variable and baseline MAP, age, sex, body weight, and family history of hypertension as independent variables, a regression coefficient of .564 ($P<.003$) was obtained. Stepwise regression analysis revealed that only age, body weight, and family history of hypertension contributed significantly to the multiple regression. With age alone, the regression coefficient was .409; when body weight was added, r was .498, and with the additional inclusion of family history, r rose to .556.

The reproducibility of our procedure to determine salt sensitivity was reexamined in 31 subjects. The response to the changes in salt intake was found to be different in 3 subjects compared with the first study. Whereas all the salt-sensitive subjects again had a fall in MAP of at least 5 mm Hg during salt restriction, one counterregulator had to be classified as salt resistant in the second study. Of the previously salt-resistant subjects, one was found to be salt sensitive and another to react like a counterregulator in the second study. In the 31 reexamined subjects, the change in MAP between low- and high-salt intake was 2.8±1.1 mm Hg in the first study and 2.5±0.9 mm Hg in the second. The changes in MAP in the first and second studies were significantly correlated ($r=.71$, $P<.001$).

In all groups of subjects, PRA and plasma concentrations of aldosterone and norepinephrine were stimulated during low-salt intake, whereas plasma concentrations of ANP increased during the high-salt diet (Table 6). At baseline as well as during low- and high-salt intake, PRA and plasma concentrations of aldosterone were significantly lower in salt-sensitive compared with salt-resistant and counterregulating subjects. The rise in PRA during salt restriction was steeper in the counter-

TABLE 5. Response to Low- and High-Salt Diet According to Age

Variable	<30 Years (n=78)		30-50 Years (n=42)		>50 Years (n=43)	
	Low NaCl	High NaCl	Low NaCl	High NaCl	Low NaCl	High NaCl
Age (y)	24.9±0.3		39.8±0.8		59.9±1.1	
Body weight (kg)	68.8±1.1	69.9±1.1*	69.8±2.1	71.1±2.1*	71.7±1.9	72.9±1.9*
MAP (mm Hg)	84.8±0.7†	84.1±0.7‡	84.6±1.1	84.0±1.1§	87.2±1.1	89.6±1.2‖
Heart rate (bpm)	65.7±1†	62.7±1.1*	65.1±1.4¶	62.9±1.4#	70.2±1.5	64.6±1.5*
Urinary Na^+ (mmol/24 h)	15.5±1**	293.2±3.8*	15.9±1.3¶	291.4±5.2*	19.6±1.3	283.7±4.2*
Urinary K^+ (mmol/24 h)	76.3±1.8	71.1±1.8*	72.1±2.1	70.5±2.4	74.4±2.1	71.1±2.3‖
Serum creatinine (μmol/L)	87.5±0.9	81.3±0.9*	84.9±1.7	79.6±1.5*	88.2±1.5	82.2±1.6*
Creatinine clearance (mL/min)	106.7±2.3‡	116.5±2.8*‡	95.4±3.6††	109.1±3.2*‡‡	88.8±3.1	95.8±3.4#

MAP, mean arterial pressure; bpm, beats per minute.
*$P<.001$, low NaCl vs high NaCl.
†$P<.05$, ‡$P<.001$, <30 years vs >50 years.
§$P<.001$, 30-50 years vs >50 years.
‖$P<.05$, low NaCl vs high NaCl.
¶$P<.05$, 30-50 years vs >50 years.
#$P<.01$, low NaCl vs high NaCl.
**$P<.01$, <30 years vs >50 years.
††$P<.01$, <30 years vs 30-50 years.
‡‡$P<.01$, 30-50 years vs >50 years.

TABLE 6. Plasma Renin Activity and Plasma Concentrations of Aldosterone, Norepinephrine, and Atrial Natriuretic Peptide at Baseline and During Low- and High-Salt Intake in Study Subjects

	Salt-sensitive			Salt-resistant			Counterregulation		
Variable	Baseline	Low NaCl	High NaCl	Baseline	Low NaCl	High NaCl	Baseline	Low NaCl	High NaCl
PRA ([ng/mL]/3 h)	1.3±0.2*	5.6±0.5*	0.5±0.1†‡	2.2±0.1§	8.0±0.5§	1.3±0.1†	2.8±0.3‖	12.0±1.4‖	1.5±0.2†‖
Aldosterone (pg/mL)	59.0±3.4¶	235.9±21.8*	40.7±3.5*‡	80.9±4.0	308.7±13.7	54.7±2.5†	93.3±8.8#	353.4±34.8#	54.8±4.8†**
Norepinephrine (pg/mL)	329±42	423±44	295±32†	302±22	457±47	330±28†	290±34	390±39	283±30††
ANP (pg/mL)	49.0±4.9	37.3±4.8	85.2±1.5†‡	42.9±2.8	27.6±2.4	46.1±2.8†	36.8±4.2	24.8±3.2**	46.3±7.1†#

PRA, plasma renin activity; ANP, atrial natriuretic peptide.
*$P<.001$, salt-sensitive vs salt-resistant.
†$P<.001$, low NaCl vs high NaCl.
‡$P<.001$, salt-sensitive vs salt-resistant.
§$P<.05$, salt-resistant vs counterregulation.
‖$P<.001$, salt-sensitive vs counterregulation.
¶$P<.01$, salt-sensitive vs salt-resistant.
#$P<.01$, salt-sensitive vs counterregulation.
**$P<.05$, salt-sensitive vs counterregulation.
††$P<.01$, low NaCl vs high NaCl.

regulating subjects than in the two other groups. The increase in plasma ANP concentrations during high-salt intake was clearly most pronounced in the salt-sensitive subjects. No differences in plasma norepinephrine concentrations among the groups could be observed. At baseline and during high-salt intake, PRA in subjects older than 50 years was lower ($P<.05$) (1.7±0.2 and 0.9±0.2 ng/mL per 3 hours, respectively) than in subjects younger than 30 years (2.3±0.2 and 1.4±0.1 ng/mL per 3 hours, respectively). Plasma concentrations of norepinephrine at baseline and during low- and high-salt intake were higher ($P<.001$) in subjects more than 50 years of age (437±39, 602±57, and 436±36 pg/mL, respectively) than in those between 30 and 50 years of age (253±29, 375±38, and 253±23 pg/mL, respectively) and those less than 30 years of age (253±16, 346±31, and 253±19 pg/mL, respectively). Also, plasma concentrations of ANP at baseline and during low- and high-salt intake were higher ($P<.001$) in the older subjects (64.9±6.5, 48.1±5.8, and 81.8±7.1 pg/mL, respectively) compared with subjects between 30 and 50 years of age (43.1±3.3, 28.9±2.8, and 49.3±3.4 pg/mL, respectively) and those younger than 30 years (36.3±2, 21.3±1.3, and 37.1±2.2 pg/mL, respectively). Otherwise, no differences in the hormonal responses to low- and high-salt intake could be observed when the subjects were subgrouped according to age, gender, and family history of hypertension.

Discussion

In the present study, the responses of blood pressure and hormonal variables to changes in dietary salt intake were investigated in 163 nonobese normotensive subjects. Of these subjects, 18.4% were found to be salt sensitive. Salt sensitivity was arbitrarily defined as a rise in MAP of at least 5 mm Hg when subjects changed from a low- to a high-salt diet. In an almost equal number of subjects (15.3%), who were termed counterregulators, MAP fell by at least 5 mm Hg under the same conditions. When all subjects are taken together, blood pressure was not influenced by the dietary changes. The reexamination of 31 subjects demonstrated that the present procedure of investigating the response to changes in dietary salt intake was reliable and reproducible in more than 90% of the subjects studied.

Salt sensitivity is a well-known phenomenon and has been observed in both hypertensive and normotensive subjects.[8] It has been suggested that the level of salt intake plays an important role in the pathogenesis of essential hypertension.[1,2] Salt-sensitive subjects may be especially prone to developing hypertension, as Weinberger and Fineberg[15] observed a steeper rise in blood pressure over time in salt-sensitive than in salt-resistant subjects.

The response to salt restriction appears to be linked to the height of blood pressure.[8] Therefore, salt sensitivity can be observed in higher frequency in hypertensive than in normotensive subjects. Applying a method of rapid sodium and volume expansion and contraction, Weinberger et al[8] classified 26% of their normotensive and 51% of their hypertensive subjects as salt sensitive. In a number of previous but much smaller studies, a similar prevalence (approximately 50%) of salt sensitivity in hypertensive patients has been described.[16-18] With a study protocol similar to ours, Sullivan and Ratts[19] observed salt sensitivity in 92 normotensive subjects with a frequency (16.3%) similar to ours. In the same study, salt sensitivity was found in 29.2% of 65 borderline hypertensive subjects.

The present and previous studies demonstrate that the blood pressure response to salt restriction is heterogeneous and not uniformly a depressor one. Longworth et al[9] observed in 30 of 82 hypertensive patients increases in MAP ranging from 1 to 25 mm Hg when dietary NaCl was mildly restricted from 197 to 70 mmol/d, and MAP rose by more than 5 mm Hg in 7 of 25 patients when sodium intake was restricted to 10 to 15 mmol/d. In the study of Egan et al,[20] 5 of 9 normotensive and 6 of 18 hypertensive subjects exhibited an increase in MAP of 5% or higher when changing from high- to low-salt intake. Similar responses, although less frequently, can be derived from the data obtained by Weinberger et al[8] and Sullivan and Ratts.[19] From their results it can be concluded that an increase in blood pressure during salt depletion is more often

found in normotensive than in hypertensive subjects. Because of this heterogeneous response to salt restriction, especially in normotensive subjects, a rise in blood pressure has not been uniformly described when subjects changed from a low- to high-salt diet.[20,21] Similarly, in the present study, blood pressure remained unchanged when all subjects were analyzed together.

Family history of hypertension is thought to be one of the determinants of salt sensitivity.[15,22] In a study of Skrabal et al,[22] 8 of 12 normotensive subjects responding to salt restriction with a fall in systolic or diastolic pressure of at least 5 mm Hg had a positive family history of hypertension. Sharma et al[23] described salt sensitivity in 68% of normotensive subjects with a positive and in only 20% of those with a negative family history of hypertension. Supporting a role for genetic involvement, Miller et al[24] showed genetic similarities in the blood pressure response to dietary salt restriction. In contrast, Watt et al[25] and Dimsdale et al[26] failed to observe an effect of family history of hypertension on the response to salt depletion. Moreover, in the study of Sullivan and Ratts,[19] salt-resistant normotensive subjects tended to have a positive family history more often than their salt-sensitive counterparts. In the present study, subjects with a positive family history had a significantly higher blood pressure at baseline and were salt sensitive more often than those with a negative family history. In contrast, subjects with a negative family history exhibited a rise in blood pressure during sodium restriction more often than those with a positive family history. Accordingly, multiple regression analysis revealed that a family history of hypertension contributed significantly to the diet-induced changes in blood pressure. Because the frequency of salt sensitivity seems to rise with age and because subjects with a positive family history were younger than those with a negative family history of hypertension, the contribution of genetic predisposition to salt sensitivity may even have been underestimated in the present study.

It has been suggested that the rise in blood pressure with age is due to a high-salt intake and that salt sensitivity is more prevalent in older age groups.[27] This suggestion is not undisputed, because in the studies of Umeda et al[28] and Dimsdale et al[26] age was not a predictor of salt sensitivity. However, the results of Weinberger and coworkers[8,15,29] demonstrate a relation between age and sodium sensitivity. Weinberger and Fineberg[15] concluded from their work that salt sensitivity is related to the age-associated increase in blood pressure characteristic of industrialized societies and that it can be shown to be a predictor of subsequent age-related blood pressure increases. In the present study, baseline blood pressure correlated with age, as expected. In addition, the change in blood pressure after low- and high-salt intake was related to age. Salt sensitivity was more prevalent in the older age group, whereas in the younger age group an increase of blood pressure with salt restriction was observed more often than a fall. Of the parameters included in multiple regression analysis, age showed by far the largest contribution to the change in blood pressure between low- and high-salt intake.

To avoid possible effects of obesity and hyperinsulinemia on the blood pressure response to changes in dietary salt intake, we included only nonobese subjects in the present study. Rocchini et al[30] recently observed a significant fall in blood pressure when subjects switched from a high- to a low-salt diet in obese but not in lean subjects. In addition, salt sensitivity was directly related to hyperinsulinemia and was markedly suppressed after weight loss in these subjects. In the study of Dimsdale et al,[26] obese patients were more likely to increase their systolic pressure in response to salt loading than nonobese individuals. In contrast, in a study in adolescents a significant fall in blood pressure during salt restriction could be observed in lean subjects with a body mass index of less than 23 kg/m^2 but not in those with a higher body mass index.[31] In the present study in nonobese subjects, the change in blood pressure between low- and high-salt intake did not correlate to body mass index, but it was inversely related to body weight. This may partly be secondary to the fact that the women in our study, who had a significantly lower body weight, were more often salt sensitive and exhibited less often a rise in blood pressure after salt restriction than the men. On the other hand, sex differences did not contribute significantly to the change in blood pressure in multiple regression analysis. The findings on sex differences with regard to salt sensitivity are not consistent.[32] In the INTERSALT study,[33] the association between sodium and blood pressure tended to be more marked in women than in men, whereas Khaw and Barrett-Connor[34] found a more pronounced association in men. Weinberger et al[8] observed no sex differences at all.

In the present study, salt-sensitive subjects exhibited the lowest PRA and plasma aldosterone concentrations at baseline as well as during the low- and high-salt diets. The steepest rise in PRA during salt restriction was seen in the counterregulators. Therefore, the rise in blood pressure during low-salt intake in these subjects may be partially due to an overstimulation of the renin-angiotensin-aldosterone system. In turn, a less responsive renin-angiotensin-aldosterone system may facilitate the fall in blood pressure in salt-sensitive individuals during salt restriction. Similarly, previous studies in normotensive and hypertensive subjects have shown that the rise in PRA during low- compared with high-salt intake was more pronounced in salt-resistant than in salt-sensitive individuals.[17-19,26] Because salt-sensitive subjects in the present study were older than salt-resistant and counterregulating individuals, the differences in PRA among the groups could be partially explained by the age-dependent decrease in the activity of the renin-angiotensin system.[35]

From the observation of Campese et al,[36] who reported a significant decrease in plasma norepinephrine concentrations during high-salt intake in salt-resistant but not in salt-sensitive hypertensive patients, one may derive that an impaired suppressibility of the sympathetic nervous system may contribute to salt sensitivity. In the present study, the frequency of salt sensitivity increased with age, and similar to the present results, it has been reported that plasma norepinephrine also rises with age,[37] suggesting a link between salt sensitivity and the sympathetic nervous system. However, similar to previous observations,[19] plasma concentrations of norepinephrine were not

different among the groups. Moreover, the increase in heart rate in salt-resistant and counterregulating but not in salt-sensitive subjects during salt restriction may even point to a less responsive sympathetic nervous system in salt-sensitive subjects. Therefore, the contribution of the sympathetic nervous system to salt sensitivity remains questionable.

In the present study, plasma concentrations of ANP increased with high-salt intake, confirming earlier results.[38] This response of ANP was significantly more pronounced in salt-sensitive compared with salt-resistant and counterregulating subjects. Similar results were obtained previously in salt-sensitive hypertensive patients, who exhibited a greater rise in plasma levels of ANP in response to increasing salt intake than did salt-resistant hypertensive individuals.[39] Atrial secretion of ANP appears to be elicited by volume expansion.[38] Our data thus are consistent with the concept that the ability of the kidney to excrete a salt load is impaired in salt-sensitive subjects, resulting in greater salt and water retention and a corresponding rise in plasma ANP.[40] Because renal function decreases with age,[41] this concept may also explain why plasma ANP levels increased with age in the present and a previous study.[42]

In conclusion, in the present study of nonobese normotensive subjects, salt sensitivity was found in 18.4% and an increase in blood pressure during sodium restriction compared with salt loading in 15.3%. Age, body weight, and family history of hypertension contributed significantly to the change in blood pressure after different salt intakes. Salt sensitivity was more likely to occur in older subjects and in individuals with a lower body weight and a positive family history of hypertension. In contrast, an increase in blood pressure with salt restriction could be observed more often in younger subjects and in those with a higher body weight and a negative family history of hypertension. Women tended to be salt sensitive more often than men. At least on the short-term basis of our study, an increase in blood pressure after salt restriction in normotensive subjects was almost as likely as a decrease. This increase in blood pressure in counterregulating subjects may be partially due to an overstimulation of the renin-angiotensin-aldosterone system during salt restriction. The exaggerated response of ANP to a high-salt intake in salt-sensitive subjects may point to an impaired ability of the kidney to excrete a salt load in these subjects.

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